Social Pain and the Brain: Controversies, Questions, and Where to Go from Here

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Abstract

Emerging evidence has shown that social pain—the painful feelings that follow from social rejection, exclusion, or loss—relies on some of the same neural regions that process physical pain, highlighting a possible physical-social pain overlap. However, the hypothesis that physical pain and social pain rely on shared neural systems has been contested. This review begins by summarizing research supporting the physical-social pain overlap. Next, three criticisms of this overlap model are presented and addressed by synthesizing available research. These criticisms include the suggestions that (*a*) neural responses to social pain are indicative of conflict detection processes, rather than distress; (*b*) all negative affective processes, rather than social pain specifically, activate these pain-related neural regions; and (*c*) neural responses to social (and physical) pain reflect the processing of salience, rather than hurt. Implications of these findings for understanding social and physical pain are discussed, and key next steps are suggested.

Contents

INTRODUCTION

In the past decade, evidence has accumulated to suggest that experiences of social pain—the painful feelings following social rejection, exclusion, or loss—may rely on some of the same neural regions that process the distressing experience of physical pain (Eisenberger 2012). Although these data have been persuasive to some, they have also been met with some resistance, and lingering questions

about the specificity of these effects still remain. This review begins by highlighting the evidence for the hypothesis that social pain and physical pain rely on similar neural and neurobiological substrates. It then discusses the questions and controversies that have arisen as these data have accumulated, including: Is neural activity in response to social rejection really due to cognitive factors, such as expectancy violation? Are the neural correlates of social pain specific to social pain or more broadly linked to negative affect? Does neural activity in response to rejection merely reflect the processing of salience (defined as how much a stimulus contrasts with its surroundings or with past experiences)? Each of these questions is evaluated in light of existing data and relevant theoretical approaches. Finally, this review discusses what these emerging data mean for the study of social pain, physical pain, and emotion research more broadly and identifies the key next steps that need to be taken to better understand the pain or distress of broken social ties.

DOES SOCIAL REJECTION HURT?

Common experience tells us that events such as relationship breakups, social snubs, and losing those closest to us can be emotionally devastating. In fact, nearly 75% of people list the loss of a close relationship (through a relationship breakup or death) as the single most negative event of their lives (Jaremka et al. 2011). In many cases, individuals describe these negative social experiences as being painful and use physical pain words to capture their emotional responses to these events, complaining of *broken* hearts, *hurt* feelings, or emotional *scars*. Interestingly, this pattern of using physical pain words to describe experiences of social disconnection is not unique to the English language but can be found across many different languages and multiple continents (MacDonald & Leary 2005), suggesting a potentially universal phenomenon. But why would social rejection or loss be described as painful? Is this an important clue to the way in which social relationships are processed by the brain, or is this simply a figure of speech, not to be taken too literally?

Over the past 10 years, researchers have investigated these precise questions (Eisenberger 2012, Eisenberger & Lieberman 2004, Eisenberger et al. 2003, MacDonald & Leary 2005, Panksepp 1998). Based on the importance of social ties for human survival, the physical pain signal—which captures attention and alerts us to potential or actual damage to the physical body—may have been co-opted by the social attachment system to alert us to potential or actual damage to our social relationships (Panksepp 1998). Indeed, this type of signaling mechanism may be particularly critical for mammalian species that rely on close others for survival. Early on, mammalian infants are almost completely dependent on caregivers for nourishment and protection. Later on, connections to others (in the social group) continue to aid survival through shared responsibilities for protection, food acquisition, and care of offspring. Given this profound dependence on others for survival, separation from others represents a serious risk to physical safety and survival and hence may be processed by some of the same mechanisms that process threats to physical safety. Researchers have hypothesized that there is a physical-social pain overlap, such that social pain—the unpleasant experience associated with actual or potential damage to one's sense of social connection or social value—may be processed by some of the same neural circuitry that processes physical pain (Eisenberger 2012, Eisenberger & Lieberman 2004, Eisenberger et al. 2003, MacDonald & Leary 2005, Panksepp 1998).

EVIDENCE FOR A PHYSICAL-SOCIAL PAIN OVERLAP

Pharmacological Evidence

The first empirical evidence for a physical-social pain overlap came from the study of opioid processes in animals. Panksepp (1998) proposed that the opioid system, well known for its role in

both euphoria and pain relief, may have been co-opted to facilitate social bonding processes. He proposed that social bonding processes altered endogenous opioid activity such that social bonding increased endogenous opioids and elicited pleasant feelings of connection, whereas social separation reduced endogenous opioids, leading to reduced feelings of social connection and increases in pain and distress. Indeed, his and others' experimental work demonstrated that nonsedating amounts of morphine, an opioid agonist known for its pain-relieving properties, could reduce distress vocalizations emitted by immature animals following maternal separation (Herman & Panksepp 1978, Kalin et al. 1988, Panksepp et al. 1978). Likewise, naloxone, an opioid antagonist, can increase these distress vocalizations (Herman & Panksepp 1978).

Consistent with this evidence, mice lacking the mu-opioid receptor gene show reductions in isolation calls following maternal-infant separation (Moles et al. 2004). Moreover, in rhesus monkeys, variation in the mu-opioid receptor gene (*OPRM1*) relates to attachment behaviors in both offspring and mothers. Infants who carry the *G* allele, which is known to relate to greater physical pain sensitivity (Chou 2006, Sia et al. 2008), show increased distress upon separation from their mothers (Barr et al. 2008), and mothers who carry the *G* allele are more likely to prevent their infants from separating from them (Higham et al. 2011) (possibly because of the increased distress associated with separation). Together, these studies show that opioids may be an important shared substrate underlying physical and social pain.

Neuropsychological Evidence

In addition to pharmacological evidence, lesion studies in both humans and animals support the idea that physical and social pain rely on shared neural substrates. As a bit of background, the experience of physical pain can be subdivided into two components: (*a*) a sensory component involved in coding for pain localization (arm versus leg), quality (stinging, aching), and intensity (the strength of the nociceptive signal) and (*b*) an affective component involved in coding for the unpleasant or distressing experience of pain and the drive to terminate the stimulus causing this unpleasant experience (Price et al. 1987).

Although these two components are highly correlated (particularly at the upper ends of painful experience), observations from patients with lesions have been able to tease apart these two components and have shown that the affective component is processed cortically by the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI), whereas the sensory component is processed by primary and secondary somatosensory cortices (S1, S2) and the posterior insula (PI) (Treede et al. 1999) (see **Figure 1**). Consequently, lesions to the dACC or insula can dull the unpleasantness of pain without altering the sensory component, resulting in reports by patients that they can still localize pain but that the pain no longer bothers them (Berthier et al. 1988, Foltz & White 1962). Conversely, lesions to S1, S2, or PI lead to deficits in processing sensory information (e.g., temperature discrimination) but, in some cases, do not disrupt the affective component, leaving patients still able to report the sensations as unpleasant (Greenspan & Winifield 1992, Ploner et al. 1999). Similarly, in rodents, lesioning the anterior portion of the dACC prior to a painful formalin injection reduces behaviors related to the affective component of pain (conditioned place avoidance) but does not alter other behaviors related to the sensory component (paw lifting, licking, flinching) (Johansen et al. 2001).

Neuroimaging studies of pain have revealed similar findings. Hypnotic suggestions to increase the unpleasantness of physical pain lead to specific increases in dACC activity without altering activity in S1 (Rainville et al. 1997), whereas suggestions to increase the intensity of physical pain lead to increases in S1 without altering activity in the dACC (Hofbauer et al. 2001). Moreover, self-reports of pain unpleasantness correlate with increased activity in the dACC and AI (Tölle et al. 1999).

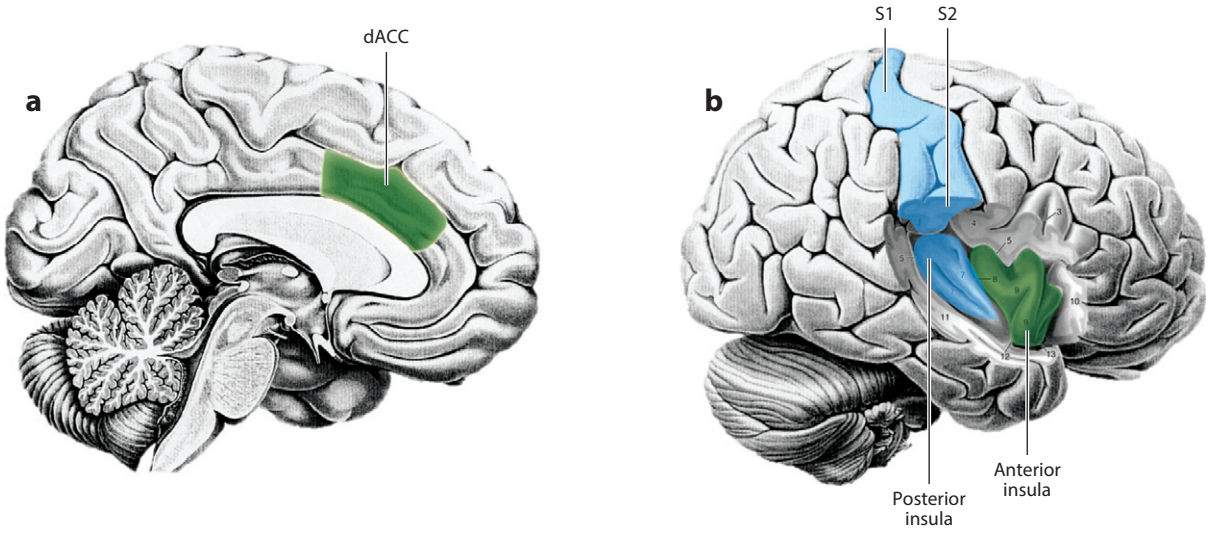


Figure 1

Cortical neural regions associated with the affective and sensory components of pain. The neural regions associated with the affective component of pain (*green*) include the dorsal anterior cingulate cortex (dACC) (*a*) and the anterior insula (*b*). The neural regions associated with the sensory component of pain (*blue*) include the posterior insula, primary somatosensory cortex (S1), and secondary somatosensory cortex (S2) (*b*).

Given the importance of the affective component of pain for signaling an aversive state and motivating behaviors to reduce or escape the source of pain, it has been hypothesized that the affective, rather than the sensory, component of pain may overlap with social pain (Eisenberger 2012, Eisenberger & Lieberman 2004). Thus, social pain should rely on affective neural regions, such as the dACC and AI, in order to warn against and prevent the dangers of social harm. Consistent with this perspective, a patient with a pain disorder that impairs the sensory but not affective component of pain (congenital insensitivity to pain) reported feeling pain for the first time after the death of a younger sibling (Danziger & Willer 2005), showing that social pain can still be felt if the affective component of pain is intact even if the sensory component is not. It is possible that sensory-related regions are also involved in social pain, as somatic symptoms are often reported following social pain (Gudmundsdottir 2009, Leary & Springer 2001), and some studies have shown activation in sensory-related neural regions (PI, S2) following social rejection (Fisher et al. 2010, Kross et al. 2011). However, given the lack of direct physical assault during a socially painful experience, it is not yet clear how sensory information, which typically arises from peripheral nociceptors, would be activated during an experience of social pain.

In line with the hypothesized role of the affective component of pain in social pain processes, animal work has shown that the ACC also plays a role in separation distress behaviors. Thus, lesioning the ACC (dorsal and/or ventral to the genu) in infant mammals reduces distress vocalizations upon mother-infant separation (Hadland et al. 2003, MacLean & Newman 1988), whereas stimulating this region leads to the spontaneous production of these vocalizations (Robinson 1967, Smith 1945). Likewise, lesioning the cingulate cortex in mothers also impairs maternal behavior in some species, such that mothers no longer engage in pup retrieval (bringing pups back to the nest) (Murphy et al. 1981, Slotnick & Nigrosh 1975, Stamm 1955). Expanding beyond mother-infant attachment, lesions to the ACC (both dorsal and ventral to the genu) in monkeys have been shown to reduce social interactions and the amount of time spent in proximity with others. Finally, in

humans, cingulotomies (a surgical procedure that involves lesioning a portion of the dACC) can reduce shyness and lead to a reduced concern about the opinions or judgments of others (Tow & Whitty 1953). These data suggest that this region may be critical for processing the distress associated with social separation or disconnection.

Neuroimaging Evidence

Neuroimaging studies have also shown that experiences of social pain rely on affective pain-related neural regions. In the first study to explore this, participants were socially excluded during a virtual ball-tossing game, called Cyberball, that was supposedly played with two other individuals (Eisenberger et al. 2003). In response to social exclusion (versus inclusion), participants showed increased activity in the dACC and AI. Moreover, greater reports of social distress (feeling rejected, meaningless) were associated with greater activity in the dACC. Since that initial study, several other studies have shown that other forms of socially painful experience, such as experiencing the threat of negative social evaluation (Eisenberger et al. 2011a, Takahashi et al. 2009, Wager et al. 2009), viewing rejection-related images (Kross et al. 2007), reliving a romantic rejection (Fisher et al. 2010, Kross et al. 2011), or being reminded of a lost loved one (Gündel et al. 2003, Kersting et al. 2009, O'Connor et al. 2008), activate these neural regions as well. In addition, one study demonstrated that participants showed overlapping neural activity in both affective (dACC, AI) and sensory (PI, S2) regions in response to a physical pain task and a social pain task (Kross et al. 2011).

Finally, several factors known to increase sensitivity to social pain, such as low self-esteem (Onoda et al. 2010), anxious attachment (DeWall et al. 2012), and interpersonal sensitivity (Eisenberger et al. 2007b), have been shown to be associated with greater dACC and/or AI activity to social exclusion. Likewise, factors known to reduce sensitivity to social pain, such as social support (Eisenberger et al. 2007a, Masten et al. 2012) and avoidant attachment (DeWall et al. 2012), have been associated with reduced dACC and/or AI activity to social exclusion. Together, these studies support the hypothesis that physical and social pain overlap in their underlying neural substrates.

Consequences of an Overlap

To the extent that physical and social pains rely on shared neural substrates, one expected consequence is that individuals who are more sensitive to one kind of pain should also be more sensitive to the other. Indeed, clinical reports reveal that patients with chronic pain are more sensitive to social pain (Asmundson et al. 1996) and that those who tend to be more sensitive to social pain also report more somatic symptoms, including pain (Ciechanowski et al. 2002, Ehnvall et al. 2009, Waldinger et al. 2006). Experimental studies have shown that individuals who are more sensitive to experimental pain self-report higher levels of social pain in response to social exclusion (Eisenberger et al. 2006). Likewise, participants with a genetic polymorphism linked with physical pain sensitivity (the *G* allele of *OPRM1*) report higher levels of rejection sensitivity and show greater activity in the dACC and AI in response to social exclusion (Way et al. 2009).

A second hypothesized consequence of a physical-social pain overlap is that factors that increase or decrease sensitivity to one kind of pain should have a parallel effect on the other kind of pain. Hence, patients who report more early social trauma tend to experience more physical pain later in life (Brown et al. 2005, Landa et al. 2012), and inducing social exclusion or failure has been shown to increase physical pain sensitivity (Bernstein & Claypool 2012, Levine et al. 1993, van den Hout et al. 2000; cf. DeWall & Baumeister 2006). Likewise, factors that decrease social pain, such as social support, also decrease physical pain. Individuals who have more social support tend to experience less pain (Kulik & Mahler 1989, Zaza & Baine 2002), and viewing a picture or holding

the hand of a loved one reduces self-reported pain and pain-related neural activity (dACC, AI) to experimental pain stimuli (Eisenberger et al. 2011b, Master et al. 2009, Younger et al. 2010).

Additionally, factors that alter physical pain have similar effects on social pain. Inflammatory activity, which is the immune system's first line of defense against foreign agents and is known to increase physical pain sensitivity, can also increase self-reports of social disconnection (Eisenberger et al. 2010). Moreover, greater increases in inflammatory activity are associated with increased dACC and AI activity in response to social exclusion (Eisenberger et al. 2009). Likewise, Tylenol® (generic names: acetaminophen, paracetamol), which is known to reduce physical pain, has been shown to reduce hurt feelings as well as dACC and AI activity in response to social exclusion (DeWall et al. 2010).

Summary

Multiple lines of research support the hypothesis that physical and social pain rely on shared neurochemical and neural substrates. To be clear, these findings should not be taken as evidence that physical and social pain are the same thing, as people can clearly discriminate between a physical injury and a social snub, but rather that there is a shared experiential and computational element—the feeling of distress or suffering and the motivation to put this experience to an end. The next section reviews the controversies that have arisen in response to the study of this hypothesized physical-social pain overlap.

CONTROVERSIES AND CRITICISMS OF THE PHYSICAL-SOCIAL PAIN OVERLAP MODEL

The criticisms of the physical-social pain overlap model have shifted across the past decade and seem to have largely grown out of the dominant psychological model in place at the time. For example, when the first social exclusion paper was published in 2003 (Eisenberger et al. 2003), it was set to the background of a cognitive account of dACC function, highlighting this region's role in certain cognitive processes, such as conflict monitoring and discrepancy detection (Botvinick et al. 2004), whereas the rostral-ventral portion of the ACC was thought to be primarily involved in affective processes (Bush et al. 2000). Early on, this led to the criticism that the dACC response to the Cyberball exclusion task was not a function of the distressing experience of social rejection but rather was a by-product of the fact that the task involved an expectancy violation (being unexpectedly excluded). Interestingly, more recently, the pendulum of criticisms has swung to the other extreme. Perhaps resulting from several recent meta-analyses showing that the dACC and AI activate in response to various types of negative affect (Kober et al. 2008, Shackman et al. 2011), the criticisms have shifted from those suggesting that the role of the dACC in social pain can be explained by simple cognitive processes to those suggesting that the role of the dACC in social pain can be explained by simple affective processes or even by the simple detection of salience. The following sections examine each of these criticisms, review the background that led to the criticism, and discuss the implications of each criticism for the physical-social pain overlap model.

CONTROVERSY #1: THE DORSAL ANTERIOR CINGULATE CORTEX IS SPECIALIZED FOR COGNITIVE (NOT AFFECTIVE) PROCESSING AND THUS DOES NOT REFLECT THE PAIN OF SOCIAL REJECTION

Background

Throughout the late 1990s and early 2000s, a flurry of cognitive neuroscience research was aimed at delineating the computational substrates of dACC activity. This was due, in large part, to the

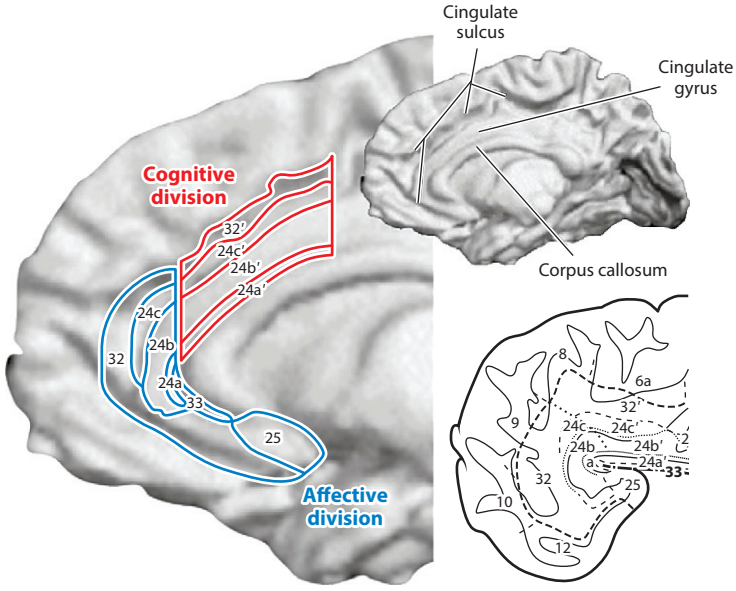


Figure 2

The hypothesized subdivision of the anterior cingulate cortex into a dorsal cognitive division and a rostral-ventral affective division. Adapted from Bush et al. (2000), with permission from Elsevier.

fact that many different kinds of cognitive tasks elicited activation in this region. Through a series of elegant neuroimaging studies and computational approaches, Cohen, Carter, and Botvinick (reviewed in Botvinick et al. 2004) demonstrated that dACC activation in response to these different tasks could be explained by one function: the detection of conflicts in information processing. Connecting this computational explanation with a larger theoretical account, these researchers proposed that the dACC served to detect conflicts or discrepancies in information processing in order to trigger separate cognitive control processes aimed at resolving the conflict. Multiple studies have supported this idea, demonstrating the involvement of the dACC in conflict monitoring or discrepancy detection and other regions such as the dorsolateral prefrontal cortex in instantiating cognitive control in order to resolve the conflict (Carter et al. 1998, 2000; MacDonald et al. 2000).

These findings likely inspired an influential account of ACC function that proposed that the dACC was predominantly involved in cognitive processes, whereas the rostral-ventral ACC (the region of the ACC anterior and inferior to the genu of the corpus callosum) was predominantly involved in affective processes (Bush et al. 2000; see **Figure 2**). Although this proposal has continued to shape interpretations of dACC and rostral-ventral ACC activity, it is important to note that this account was based on a restricted review of the literature. Many of the affective studies reviewed for this account came from clinical populations, which often show nonnormative affective responses. Moreover, findings from pain studies were explicitly excluded from this synthesis. Thus, although much of the early work on dACC function suggested a role for the dACC in affective and pain processes (Foltz & White 1962, Tow & Whitty 1953), these findings were not integrated into this account of dACC function.

On the basis of this cognitive model of dACC function, early criticisms of the social pain findings suggested that the dACC response to the Cyberball task was not due to the experience of social

pain per se, but rather to the fact that the Cyberball task induces an expectancy violation—which could be seen as a conflict or discrepancy in information processing. Specifically, the Cyberball task violates subjects' expectations by including them for a period of time and then excluding them.

Somerville and colleagues (2006) were the first to test this expectancy violation hypothesis. These authors hypothesized that the ventral or subgenual ACC (subACC) would respond to social rejection, whereas the dACC would respond to expectancy violation. To examine this, they used a social feedback paradigm in which participants were told that they would be rating other people and that they would learn what these other people thought about them. Participants saw multiple pictures of target faces, were asked whether or not they would like the target person, and were then shown feedback about whether or not the target liked them. The authors defined rejection trials as any trials in which the target did not like the participant and expectancy violation trials as any trials in which the participant's and target's responses did not match. Results showed increased dACC activity during the expectancy violation (in comparison with congruent) trials and increased subACC activity during the social acceptance (in comparison with rejection) trials.

On the basis of this study alone, one might conclude that the dACC response to social exclusion reflects the simple processing of an expectancy violation rather than the experience of social pain. However, accumulating evidence has suggested that this is not the case. The next section presents evidence that the dACC response to social exclusion is not simply due to the processing of an expectancy violation by showing that (*a*) the dACC is known to process pain and negative affect in addition to conflict detection, (*b*) dACC lesions consistently reduce pain and negative affect but do not consistently alter conflict detection processes, and (*c*) tests of the expectancy violation hypothesis that also examine affective experience show that dACC activity is more closely aligned with the distress of rejection than with cognitive forms of expectancy violation. After reviewing these studies, I present a larger, theoretical model, which attempts to show that expectancy violation and distress may not be competing accounts of dACC activation but rather may work together as two components of a neural alarm system.

Is the dACC a Cognitive Region?

Subsequent to the influential cognitive account of dACC function, recent reviews have shown that the dACC is not simply specialized for cognitive processing but instead plays a role in both pain and negative affect. In a meta-analysis of 192 studies involving nearly 3,000 participants, Shackman and colleagues (2011) examined which regions of the ACC activated in response to (*a*) tasks that induced negative emotional states (fear/anxiety, anger, disgust, sadness); (*b*) tasks that involved the delivery of physically painful stimuli; and (*c*) tasks that involved conflict monitoring and discrepancy detection (e.g., Stroop, Go/No-Go). To the extent that the dACC is a cognitive region, one would expect that the conflict tasks would activate the dACC, whereas the affective and pain tasks would activate the rostral-ventral ACC. However, Shackman and colleagues found that all three types of tasks (negative affect, pain, and conflict) led to increased activity in the dACC. Another review (Etkin et al. 2011) of this literature came to a very similar conclusion, suggesting that the dACC is involved in the appraisal and expression of negative affect, whereas the rostral-ventral ACC is more strongly involved in regulating (reducing) negative affect. Hence, more recent reviews of the literature suggest that the dACC is not solely involved in cognitive processing and instead plays a role in processing pain and negative affect as well. Indeed, this fits with early accounts of the dACC as an affective region (Papez 1937) and is consistent with

many studies highlighting a role for this region in the perceived unpleasantness of physical pain (Apkarian et al. 2005).

Interestingly, lesion studies suggest that the role of the dACC in pain and negative affect may be more fundamental than its role in conflict monitoring. Whereas it is well known that dACC lesions consistently reduce pain unpleasantness (Foltz & White 1962, Johansen et al. 2001) and various forms of negative affect (Tow & Whitty 1953, Whitty et al. 1952), they show no consistent effects on conflict detection tasks (e.g., the Stroop task). The majority of these studies show no effect of dACC lesions on cognitive task performance (Ballantine et al. 1977, Corkin et al. 1979, Fellows & Farah 2005, Swick & Turken 2002, Vendrell et al. 1995), although some show effects that resolve over time (Cohen et al. 1999, Janer & Pardo 1991), and a few find impairments (Stuss et al. 2001, Swick & Jovanovic 2002). Moreover, although dACC activation to physical pain is commonly observed across humans and animals (Apkarian et al. 2005, Johansen et al. 2001), some evidence suggests that the dACC response to conflict monitoring may be uniquely human, as monkeys do not show dACC activation in response to cognitive conflict (Emeric et al. 2008, Ito et al. 2003, Mansouri et al. 2007, Nakamura et al. 2005; see also Cole et al. 2009). Hence, the role of the dACC in pain unpleasantness and negative affect may be more primary than its role in conflict monitoring.

Testing the Expectancy Violation Hypothesis

If it is true that the dACC plays a role in pain unpleasantness and negative affect, why did Somerville and colleagues (2006) observe that the dACC was sensitive to expectancy violation and not social rejection? There are several possible reasons. First, from a psychological or experiential perspective, the rejection and expectancy violation trials may not have been properly categorized. Thus, the rejection condition included trials (half of the total number) that might not elicit feelings of rejection: trials in which both the participant and target do not like each other, which seems more like mutual dislike or disinterest than rejection. Similarly, the expectancy violation condition included trials (half of the total number) that would likely trigger feelings of rejection: trials in which the participant likes the target but the target doesn't like the participant. The authors did not report neural activations separately for each of these different condition types, so it is not clear if, for example, the dACC activation to discrepancy detection was driven by the trials that may have induced an experience of rejection.

A related issue is that the authors did not measure how participants felt in response to each of these trial types. Thus, it is not clear if participants felt more rejected following the trials that the authors included in their rejection condition than in the trials included in the expectancy violation condition. Moreover, given that each participant completed 240 trials, it is also not clear whether participants still believed that they had actually been evaluated by the end of the task or whether they continued to be affected by the social feedback. Although this study attempted to delineate expectancy violation from rejection in the ACC, a potential lack of face-valid conditions and an absence of information on participants' experience interfere with the conclusions that can be drawn from this study.

In an effort to iron out some of these issues, Cooper and colleagues (2014) assessed both neural activity and self-reported responses to a real-world social feedback paradigm. In this study, participants went through real speed-dating sessions, indicated which partners they would be interested in seeing again, and then, in a separate scanning session, were given feedback about whether each partner was interested in them or not. Critically, subjects were asked to self-report on how happy they felt after each trial type, and the authors reported data from each condition:

(*a*) match, in which both the participant and the partner said yes to the question, "Would you be interested in seeing this partner again?"; (*b*) rejection, in which the participant said yes but the partner said no; (*c*) unrequited, in which the participant said no but the partner said yes; and (*d*) disinterest, in which both the participant and the partner said no.

Results showed that participants reported the lowest levels of happiness during their rejection condition [note that Somerville et al. (2006) included this in the expectancy violation condition] and the highest levels of happiness during the disinterest condition [a condition that Somerville et al. (2006) included in their rejection condition]. Importantly, when examining neural activity to each of these conditions separately, they found that their rejection trials (relative to the disinterest trials, matched based on the "no" response from the partner) led to increased activation in the dACC. They also found that the match trials (relative to unrequited, which matches the "yes" response from the partner) led to increased activity in the subACC/ventromedial prefrontal cortex in a region very similar to what was observed in Somerville and colleagues' study during their acceptance trials. This study highlights the importance of considering participants' self-reports and shows that the subjective negative response to social rejection is what seems to map most closely with activity in the dACC.

Another study explicitly tested the expectancy violation hypothesis by altering the parameters of the Cyberball task. Kawamoto and colleagues (2012) had participants complete the Cyberball task supposedly with two others. In addition to including the standard inclusion and exclusion conditions, the authors also added a condition that controls for the expectancy violation inherent during exclusion: an overinclusion condition, in which participants received the ball more than they expected (instead of less than they expected during social exclusion). Results indicated that subjects reported feeling significantly more social pain during the exclusion blocks relative to the inclusion or the overinclusion blocks, and exclusion led to increased activity in the dACC and AI, but overinclusion did not. Moreover, when directly comparing exclusion to overinclusion, there was still significant activation in the dACC. Indeed, similar results have been reported elsewhere, showing greater dACC activity during Cyberball social exclusion (versus inclusion) compared to a simple expectancy violation task (versus no expectancy violation) (Bolling et al. 2011). Together, these studies suggest that dACC responses to social exclusion are more indicative of an underlying experience of social pain rather than the simple cognitive processing of expectancy violation.

Finally, several other studies, though not explicitly testing the expectancy violation hypothesis, provide evidence that dACC activity to social pain is not simply due to expectancy violation. For example, in two separate studies, participants showed increased activity in the dACC (and AI) in response to reliving a romantic relationship breakup (Fisher et al. 2010, Kross et al. 2011). In both of these studies, participants knew ahead of time that they were going to be asked to reflect on these breakups during the scanning session, so there was nothing unexpected about the task; however, reliving the rejection experience still led to increased activity in the dACC. Likewise, it has also been shown that rejection sensitivity, the tendency to expect to be rejected, was associated with increased dACC activity in response to viewing disapproving facial expressions, cues which signify the possibility of social rejection (Burklund et al. 2007). If the dACC were simply sensitive to expectancy violations, we would predict that those who most expect rejection would show less activity in the dACC in response to rejecting cues, but that is not what was observed.

These studies suggest that the dACC is not solely involved in cognitive processing and instead plays a role in responding to pain and negative affect as well. However, the studies reviewed here also suggest that the assumption that the dACC is involved *either* in discrepancy detection *or* negative affective experience may be a mischaracterization, and the fact that these processes activate overlapping neural regions may suggest that they share similar or complementary functions.

Hence, rather than discrepancy detection and emotional distress being competing accounts of dACC function, they may actually be complementary.

The dACC as a Neural Alarm

Results from cognitive neuroscience research showing that the dACC is critical for conflict monitoring and discrepancy detection (Botvinick et al. 2001, 2004) combined with findings from pain and affective neuroscience research showing that the dACC is critical for the unpleasantness of physical pain (Apkarian et al. 2005, Eisenberger & Lieberman 2004, Shackman et al. 2011) suggest that the dACC may function as a type of neural alarm system (Eisenberger & Lieberman 2004, Spunt et al. 2012). For an alarm system (e.g., a smoke alarm) to function properly, two components are needed: a discrepancy detection system that monitors for deviations from desired standards (e.g., too much smoke) and a sounding mechanism (e.g., an alarm bell ringing) that alerts one to the fact that there is a problem that needs to be addressed. In the context of social experience, this alarm may monitor for inputs that suggest damage to social relationships and may result in the experience of social distress in response to the possibility or presence of broken social bonds.

Although discrepancy detection processes and distress are not typically examined together, several lines of research support the possibility that the dACC is involved in both of these processes and suggest that the process of conflict and error detection could represent a computational underpinning of affective and pain processing (Yeung et al. 2004). For example, several studies have shown that the magnitude of the error-related negativity (ERN)—an event-related brain potential that responds to conflicts or discrepancies such as error trials and is source localized to the dACC—is associated with various features of negative affect. Larger ERN responses are associated with higher levels of state and trait negative affect (Luu et al. 2000) and greater increases in autonomic and startle responses (Hajcak & Foti 2008, Hajcak et al. 2003). Moreover, individuals with negative affect-related psychopathologies show higher ERN responses to performance errors (Chiu & Deldin 2007, Fitzgerald et al. 2005, Olvet & Hajcak 2008, Weinberg et al. 2010). In addition, functional magnetic resonance imaging (fMRI) studies have shown that dACC responses to cognitive performance tasks are positively correlated with autonomic responses (Critchley et al. 2005) and the self-reported desire to avoid a task (McGuire & Botvinick 2010). Finally, a recent study demonstrated that within-subject variability in dACC responses to error trials on a stop-signal task correlated directly with self-reports of negative affective responses to the task (Spunt et al. 2012). Thus, across multiple studies, individual differences in neural sensitivity to discrepancies or errors have been shown to correlate directly with various measures of negative affective experience, supporting the alarm system model. Studies are needed to determine whether the same neural regions respond to both discrepancy detection and pain/distress or whether these are separable computational components that are instantiated in adjacent regions of the dACC.

Summary

Although a cognitive interpretation of dACC function was a natural extension of the findings generated from cognitive neuroscience research throughout the 1990s, it now seems clear that this region is involved in more than just cognitive processing. Indeed, the dACC is now known to play a larger role in pain and affective processing as well. In fact, a closer look at the literature seems to highlight a primacy for the involvement of the dACC in pain and negative affect and suggests that instead of asking why social exclusion activates a neural region involved in conflict detection, it may be more appropriate to ask why conflict detection activates a neural region involved in pain unpleasantness. Hence, the role of the dACC in conflict monitoring may actually be a by-product of its evolutionarily older role in regulating responses to threatening situations

such as those associated with pain, social exclusion, or negative affect. Studies are needed to more carefully explore these possibilities.

CONTROVERSY #2: SOCIAL REJECTION ACTIVATES THE DORSAL ANTERIOR CINGULATE CORTEX BECAUSE ALL NEGATIVE AFFECT ACTIVATES THIS REGION

Background

Following the perspective that the dACC was primarily a cognitive processing region came a series of papers showing that this region played a larger role in affective processing (Etkin et al. 2011, Mechias et al. 2010, Shackman et al. 2011). In light of these additional data, the pendulum of criticism swung to the other side and a new question emerged: Does the dACC respond to social rejection because of its role in pain unpleasantness or simply because it is involved in processing all negative emotional experience? In other words, is there anything specific about the role of the dACC in processing physical and social pain, or is this region more generally responsive to all negative emotions? Taking this question to its logical end, the primary issue is whether social rejection can be compared to physical pain or whether it is primarily an emotional experience, which typically has been distinguished from physical pain.

Note that it may be mistaken to imply that an experience is either emotional or painful; this idea may stem from a flawed understanding of physical pain processes. From an intuitive perspective, pain feels like a physical experience—a problem with the body. Because of this subjective experience, physical pain is often conceptualized as a bodily process, whereas emotional experience is conceptualized as a mental process. However, years of research have demonstrated that this intuition is misplaced. The distressing experience of physical pain that infuses pain with its aversive nature and motivates people to escape the pain is processed neurally, such that lesioning the regions responsible for this perceived unpleasantness leaves individuals unbothered by what would normally be painful sensations (Foltz & White 1962). Pain distress is mental, just like emotional distress is mental. However, the idea that pain experience is more physical than emotional is so pervasive that most medical textbooks and early models of pain incorrectly categorized physical pain as a component of physical touch, an exteroceptive modality. More recent accounts (Craig 2002) have shown that pain is actually an interoceptive modality that is distinct from touch. Pain, like affective processes, provides homeostatic information that helps to regulate the condition of the body, and a key feature that distinguishes pain from touch is its inherent association with affect. Thus, pain has not only a sensory but also an affective-motivational component, which is critical for its role in maintaining the integrity of the body and ultimately survival. Although the intuitive understanding of pain conjures up a physical experience, research highlights the importance of the affective component of pain in the aversiveness of this experience and suggests that the distress of physical pain may be more similar to negative emotional experience than had been previously imagined (Craig 2002, 2003).

Acknowledging some overlap between pain unpleasantness and emotional experience, it is still important to ask whether the dACC is specific to physical and social pain or whether this region plays a broader role in processing negative emotions, and if so, whether it is partial to certain kinds of emotions. Two lines of research are relevant to this question: (*a*) meta-analyses of the neural substrates of emotion, which can help determine whether the dACC activates reliably in response to all types of negative emotions or whether dACC activity is more specific to certain kinds of negative emotions, and (*b*) animal studies that have specifically explored the effect of ACC lesions on basic social processes and nonsocial affective processes (such as anxiety to a novel environment).

Meta-Analyses of Emotion

Several meta-analyses have investigated the neural substrates of emotional processing. For the most part, these meta-analyses have reviewed studies of what are traditionally termed basic emotions (fear, anger, disgust, sadness, happiness) and have collapsed across studies that examine the perception of emotional stimuli (e.g., seeing fear faces) and studies that induce an experience of emotion (e.g., experiencing fear). Thus, in these meta-analyses, there is not always a direct focus on the neural regions engaged when one is experiencing a particular emotional state, but rather an attempt to understand the neural underpinnings of emotional processing associated with both perceiving and experiencing a certain emotion.

One of the first meta-analyses of emotion (Phan et al. 2002) reviewed 55 positron emission tomography and fMRI studies of basic emotions and categorized these studies both by the type of emotional experience (e.g., fear, anger) as well as by the way in which the emotion was induced (visual/perceptual, auditory, emotional recall/imagery). In addition to finding some emotion-specific effects (amygdala for fear, subACC for sadness), the results also indicated that emotion manipulations involving emotional recall or imagery—which, compared to viewing negative faces, are more likely to produce a real emotional experience—tended to engage the ACC and insula (although the specific part of the ACC or insula was not specified). These early findings suggest that to the extent that emotions are experienced, as opposed to merely perceived, there is increased activity in the ACC and insula. A subsequent meta-analysis by this same group (Wager et al. 2003) examined neural activity based on emotional categories—specifically positive versus negative emotions and approach- versus withdrawal-related emotions. This study showed that an anterior portion of the dACC was specific to withdrawal-related emotions (fear, disgust, sadness), whereas the insula was activated in response to both negative emotions (fear, disgust, sadness, anger) and withdrawal-related emotions.

Two other meta-analyses investigated neural regions that were responsive to each kind of basic emotion. One meta-analysis (Murphy et al. 2003) demonstrated that although certain regions seemed specific for certain emotions (amygdala for fear; insula for disgust), the dACC was not specific to any particular emotion. The other found that the dACC showed activation to fear but not to other basic emotions (Vytal & Hamann 2010). Building on these findings, two other meta-analyses of fear- and anxiety-related emotional tasks, which tend to involve the actual experience, rather than the perception, of fear or anxiety (Etkin et al. 2011, Mechias et al. 2010), demonstrated consistent activation in the dACC as well as the AI in response to these tasks.

Finally, two recent meta-analyses examined neural responses collapsed across various emotions. Kober and colleagues (2008) found the dACC and AI to be consistently active across emotion tasks; however, this study did not examine separate neural responses to specific emotions. Interestingly, Shackman and colleagues (2011) published the only meta-analysis that examined neural responses to emotion tasks that were specifically designed to induce emotional experience. Thus, unlike the other meta-analyses, studies involving the perception of emotional faces or emotional words were not included. However, this meta-analysis reported only on data within the ACC. They found that the dACC was responsive to these emotion-inducing tasks and that the dACC was most consistently responsive in studies of fear and anxiety.

Although the studies reviewed above are not perfectly aligned, they reveal a few consistent findings. First, at a basic level, the dACC is responsive to emotional tasks. Second, when examining neural responses to different types of basic emotions, the dACC seems to be most reliably responsive to fear- and anxiety-inducing tasks (Etkin et al. 2011, Mechias et al. 2010, Shackman et al. 2011, Vytal & Hamann 2010). Moreover, this activity seems to be more frequently seen in studies that induce a real emotional experience rather than in studies that involve perceiving

emotion-related stimuli, such as emotional faces (Etkin et al. 2011, Mechias et al. 2010, Phan et al. 2002, Shackman et al. 2011). Interestingly, the consistency with which the dACC is linked with fear and anxiety is not at odds with a role for this region in physical and social pain, as threats of physical and social pain are key elicitors of fear and anxiety. Indeed, prior work has shown that the two most pressing worries of individuals with anxiety revolve around the possibility of physical harm (which involves physical pain) and the possibility of social harm (rejection, ostracism) (Beck et al. 1974). Hence, it is possible that fear of stimuli that could cause harm, either physical or social, may be central to the function of the dACC.

Still, although these meta-analyses show that the dACC is involved in emotional experience, it is not clear whether the dACC plays a more specific role in emotional experiences that result from social as opposed to nonsocial affective processes. It is possible that the dACC is responsive to certain fear-related stimuli, such as those that involve the threat of or experience of physical and social pain, but not to fear-related stimuli that do not involve physical or social pain (e.g., novel environments). Although this has not been systematically explored using human neuroimaging, it has been examined in animals.

Social and Emotional Behavior Following Lesions to the ACC

Investigations into the consequences of ACC lesions on social and emotional behavior may provide more definitive answers as to whether all negative affective experience activates the dACC. As reviewed earlier, lesions to the dACC in humans or to similar regions in animals have been shown to reduce the affective component of painful experience (Foltz & White 1962, Johansen et al. 2001). However, what is the consequence of dACC lesions for social versus nonsocial emotional behavior?

Although they did not directly examine social versus nonsocial consequences, it is interesting to note that early studies in macaques reported that following lesions to the ACC (area 24), "...the most marked change was in social behavior" (Ward 1948, p. 15). Indeed, these monkeys were described as having "lost their preoperative shyness and fear of man," as being "socially indifferent," and as having lost their "social conscience" (Ward 1948, p. 15). In fact, these monkeys seemed to no longer show acts of affection toward their companions but rather treated them as inanimate objects. Interestingly, an investigation of human subjects following cingulotomy revealed similar effects. Cingulotomies consistently reduced shyness and social inhibition and left patients with less worry as to whether they were doing the right thing in the eyes of others (Tow & Whitty 1953). Together, these studies suggest that the ACC may be associated with a concern with social belonging and a corresponding motivation to engage in behaviors that reduce the possibility of social rejection and promote social acceptance.

Building on these case studies, experimental lesion studies in animals have examined the effect of ACC lesions on social and nonsocial emotional behavior. Lesions to the ACC gyrus (dorsal and anterior to the genu of the corpus callosum) in macaques decreased the number of social interactions, time spent in proximity with others, and contact calls made between animals (Hadland et al. 2003), suggesting a role for the ACC in social motivations. Moreover, lesions to the ACC gyrus in male macaques reduced sensitivity to socially threatening figures (human making direct eye contact) as well as interest in female macaques or macaques making affiliative gestures; however, these lesions did not consistently alter nonsocial anxious behavior associated with seeing a moving snake (Noonan et al. 2010, Rudebeck et al. 2006). Similarly, ACC lesions decreased the amount of time that rats spent engaged in social interaction but did not alter other nonsocial affective processes, such as anxious responding to a novel food cue or novel environment (Rudebeck et al. 2007). These findings suggest that changes in social behavior following lesions to the ACC are

not simply the consequence of changes in anxiety. Hence, these findings suggest that this region has important consequences for social behavior that are not simply reducible to negative affective processes.

What Can We Conclude?

Does the dACC respond to social rejection because it processes all negative emotion, or is this region more specific to threats of social and physical pain or harm? At this point, it is difficult to tell for certain. Meta-analyses of emotion show that the dACC activates in response to various emotional tasks with perhaps a preference for tasks related to fear and anxiety; this pattern suggests that this region does play a role in processing emotions but is perhaps more specific to fear and anxiety. However, lesion studies show that this region may be more specific to both social processes and pain but not specific to affective responses that do not have a social component. Hence, in addition to showing clear effects on reduced pain unpleasantness, lesion studies also highlight altered social behaviors, such that individuals become less sensitive to the possibility of negative social consequences that may result in rejection. Moreover, these changes in social behavior are not the direct consequence of changes in anxiety, as ACC lesions leave certain anxiety-related behaviors (sensitivity to novelty) intact.

Thus, at this point, the question of whether the dACC responds to threats of physical and social harm specifically or whether this region is more generally sensitive to anything negative is not totally clear; additional research is needed. For now, the best answer to the question of what the dACC "cares about" may come at the intersection of research on physical pain, social pain, and emotion. Rooted in the idea that the dACC processes perceived unpleasantness (Johansen et al. 2001), it has been suggested that this region may provide an aversive teaching signal (Johansen & Fields 2004) that is critical for learning to avoid stimuli that compromise survival. Indeed, stimulating the ACC specifically can produce avoidance learning even in the absence of nociceptive input (Johansen & Fields 2004). This aversive teaching signal may be critical for motivating people to avoid physical pain, social pain, or other kinds of stimuli that could endanger survival, even in the absence of nociceptive input.

CONTROVERSY #3: THE DORSAL ANTERIOR CINGULATE CORTEX AND ANTERIOR INSULA RESPONSE TO SOCIAL (AND PHYSICAL) PAIN CAN BE EXPLAINED BY SALIENCE PROCESSING

Background

Another argument that has gained some traction recently is that the responses of the dACC and AI to social pain are not indicative of pain or distress but rather reflect the processing of salience (Iannetti et al. 2013). Salience refers to how much a stimulus contrasts with its surroundings (e.g., a red poppy in a green field) or with past experiences (e.g., the first versus fourth time a phone rings; Iannetti & Mouraux 2010). Thus, Iannetti and colleagues (Iannetti & Mouraux 2010, Iannetti et al. 2013) have suggested that although a common set of neural regions activates in response to physical pain—the so-called pain matrix, which includes the dACC, AI, PI, S1, and S2—these activations can be explained not by pain specifically but rather by cognitive processes involved in detecting, orienting toward, or reacting to salient stimuli. This perspective would help to explain why experiences such as social exclusion (Eisenberger et al. 2003) or empathy for pain (Singer et al. 2004) can activate the pain matrix without also activating nociceptors. This perspective is based on several arguments.

First, Iannetti and colleagues (2013) note that simply because the pain matrix is activated to painful stimuli does not mean that activation in these regions reflects pain processing per se. Indeed, inferring a mental process from an observed neural activation—a process known as reverse inference—is known to be logically flawed (Poldrack 2006). Thus, although neuroimaging studies can show that painful stimuli elicit activation in a certain set of neural regions, researchers cannot necessarily interpret neural activity in this pain matrix as implying the presence of pain. Instead, the validity of reverse inference depends on the specificity of the relationship between the mental state and the brain region (Poldrack 2006).

Building on the argument that the pain matrix is not actually indexing pain, Iannetti and colleagues (2013) propose that a better account is that these regions are responding to salient stimuli. To demonstrate this alternative explanation, Mouraux and colleagues (2011) conducted a study in which they used both nociceptive stimuli and salient, nonnociceptive stimuli to examine whether neural responses in the pain matrix were specific to pain or whether they showed activation to all salient stimuli. In this study, participants completed alternating tasks in which they were exposed to (*a*) nociceptive somatosensory stimuli (radiant heat that elicits a painful pinprick sensation, which is known to activate skin nociceptors); (*b*) nonnociceptive somatosensory stimuli (electrical pulses that elicit a nonpainful sensation of pricking of the skin, which is known not to activate skin nociceptors); (*c*) visual stimuli (a flashing, bright white disk); and (*d*) auditory stimuli (loud tones).

The authors found that various regions of the pain matrix were activated to each of these stimuli (relative to an implicit baseline condition) and that several of these regions correlated with self-reports of salience (defined to participants as the ability of the stimulus to capture attention). Finally, using a conjunction analysis, they showed that all four types of stimuli elicited similar patterns of neural activity in the dACC, AI, PI, S2, and thalamus. They also, however, demonstrated that neural activity in the putative pain matrix (dACC, AI, PI, S2) was significantly greater following nociceptive than nonnociceptive stimulation. They suggest that this effect was driven by the salience of the stimuli (rather than by perceived pain) because on trials when subjects rated nonnociceptive stimuli as more salient than nociceptive stimuli, neural responses in the salience network were increased. From these findings, the authors conclude that the activation of the pain matrix actually reflects the "detecting, processing, and reacting to the occurrence of salient sensory events, regardless of whether they elicit perception of pain" (Iannetti et al. 2013, p. 374).

What do we conclude from research on the salience account? Is salience a better or more accurate descriptor than 'hurt' when interpreting the neural activity that is observed in the pain matrix in response to physical and social pain? The next section reviews evidence to suggest that this salience account is not a better descriptor of neural activity in the pain matrix for the following reasons: (*a*) salience may be accounting for the exact same variance as self-reported pain unpleasantness, (*b*) predictions made from the salience perspective are not supported, and (*c*) data from lesion studies as well as reverse inference probabilities seem to show a primacy for pain experience, rather than salience, in pain matrix activation.

Does Salience Account for the Same Variance as Self-Reported Pain?

The salience account of pain matrix activation suggests that salience is a better descriptor of this activation than is pain or hurt. Indeed, when trying to find a common account for why various tasks (pain, social rejection, empathy) activate the pain matrix, the term salience seems to make sense. However, this seemingly better match of the term salience with this underlying neural activity may be a result of a lack of attention to the subjective experience of hurt or distress rather than a more accurate account of the data.

For example, in testing the possibility that salience is a better descriptor of pain matrix activity than is pain, Mouraux and colleagues (2011; described previously) asked participants to report on their experience of salience (how much a stimulus captures attention) in response to tasks (responding to nociceptive, nonnociceptive, auditory, and visual stimuli) but did not ask participants to report on their experience of pain or distress. Instead, the authors decided a priori which stimuli would count as painful on the basis of whether they were known to activate nociceptors. Given that the conscious experience of pain can occur in the absence of nociception and that the activation of nociceptors does not necessarily lead to an experience of pain (Iannetti & Mouraux 2010, Treede 2006), determining which conditions are painful without asking participants is problematic. It is plausible that a nonnociceptive pricking sensation or a very loud noise could be experienced as painful or distressing. Moreover, nociceptive and nonnociceptive trials were interspersed at random, with no warning as to which trial was about to appear, which could have increased pain unpleasantness to nonnociceptive stimuli. It is known that uncertainty about the timing of a painful stimulus can increase pain unpleasantness ratings (Oka et al. 2010, Price et al. 1980) and that expecting to receive a painful stimulus can actually increase the perceived painfulness of a nonpainful or mildly painful stimulus (Atlas et al. 2010, Sawamoto et al. 2000). Thus, it is also possible that the design of the study, which involved expecting painful stimulation on some trials but not knowing when these trials were going to occur, led subjects to experience a greater sense of pain even in response to stimuli that were not intended to be painful. Hence, without measures of self-reported pain, it is unknown whether self-reported salience accounts for the same variance as would self-reported pain experience. In order to better test this salience account, one would need to assess both self-reported salience as well as self-reported pain unpleasantness to determine whether salience does indeed provide a better account of the data.

Making Predictions from the Salience Perspective

A second issue with the salience perspective is that although the term salience seems to provide a useful descriptor for why various types of stimuli activate the pain matrix in a posthoc manner, a priori predictions made from this perspective do not seem to be supported. Based on the definition of salience (how much the stimulus contrasts with its surroundings; Iannetti & Mouraux 2010), one would expect that viewing negative emotional faces relative to neutral faces would activate the salience network—including regions such as the dACC and AI. However, these types of salient stimuli do not typically activate the pain matrix (Buhle et al. 2013, Fusar-Poli et al. 2009, Sabatinelli et al. 2011).

One might also expect that, because the term salience encompasses both positive and negative stimuli that capture attention, the presentation of both positive and negative stimuli together would lead to even greater activity in this salience network than would either presented on its own. However, participants exposed to pictures of their significant others (highly salient and positive) while experiencing physical pain (also highly salient but negative) (Eisenberger et al. 2011b, Younger et al. 2010) actually showed reduced activity in regions of the pain matrix (dACC, AI) compared to when viewing pictures of objects such as chairs (not very salient) while experiencing physical pain. Similar findings have been observed in other studies (Coan et al. 2006).

Finally, another study explicitly tested the salience hypothesis by exposing participants to a task in which they were simultaneously told about the chance of winning money (salient) and/or the chance of receiving shock (also salient) (Choi et al. 2014). Consistent with the findings from the social support studies above, instead of finding increased activity in salience-related neural regions to the combination of reward and pain together, this study found that the effect of reward was reduced during threat and that the effect of threat was reduced during reward. Hence, although

salience may provide a useful term for characterizing activations in this pain matrix posthoc, predictions from the salience perspective have not been supported.

Examining the Reverse Inference Question

Finally, Iannetti and colleagues (2013) rightfully note that inferring that pain matrix activity indicates the experience of pain is an example of reverse inference, a common mistake in which mental processes are assumed from neural activation. They argue that because the validity of reverse inference depends on the specificity of the relationship between the mental state and the brain region (Poldrack 2006) and because many different stimuli activate the pain matrix, it seems unlikely that this set of neural regions would be in any way specific for pain. However, a closer examination of this issue is warranted.

One way to approach the reverse inference issue is to examine the extent to which a region of interest is selectively activated by a psychological process of interest. To the extent that a region is activated relatively selectively by a specific process of interest, one can have more confidence in inferring that the activation of that region reflects that process. One way to investigate confidence in the reverse inference is to interrogate one of several large imaging databases to estimate the degree to which a specific brain activation implies a specific psychological process. One can then compute a posterior probability for the reverse inference, representing the likelihood that activation in this region is indicative of the process of interest.

To explore this question, we[1] have recently used a publicly available database of over 5,800 neuroimaging studies, Neurosynth (neurosynth.org; Yarkoni et al. 2011), to examine reverse inference maps for pain as well as for other salience-relevant psychological processes, including control, conflict, error, and salience. Neurosynth sorts scientific articles based on an algorithm that computes the frequency with which certain words appear in a paper. Neurosynth pulls neural activations listed in tables and inputs them into the database. The database can then compute forward inference maps on a particular topic, akin to a meta-analysis of studies on that topic, as well as reverse inference maps, which show neural regions that are more specific for that particular topic than for others.

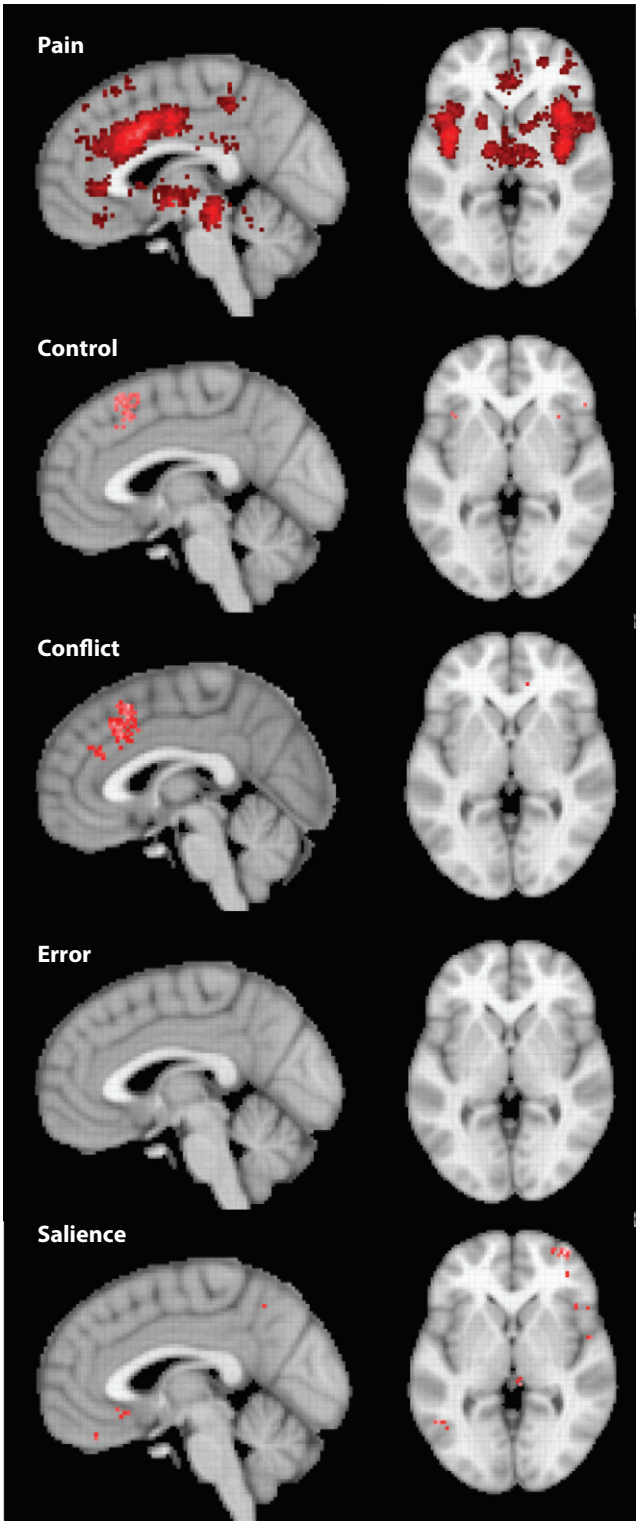
Interestingly, the reverse inference map for pain (based on 182 studies) shows widespread neural activation throughout the entire dACC and insula (AI and PI) as well as S1, S2, and thalamus, whereas the maps for other salience-related terms do not (see **Figure 3**). Hence, the reverse inference map for control (based on 231 studies) shows activation primarily in the supplementary motor area but not in these other regions; the reverse inference map for conflict (based on 51 studies) shows a region of activity in the dACC extending into the supplementary motor area but does not show activity in other regions often associated with pain; the reverse inference map for error (based on 73 studies) shows no neural activity at all; and the reverse inference map for salience (based on 6 studies) shows no activation in regions often associated with pain (dACC, AI, thalamus, etc.).

In fact, an examination of the posterior probabilities for the dACC coordinates (−4, 24, 32) that came from a meta-analysis of Cyberball social rejection studies (Cacioppo et al. 2013) showed the highest posterior probabilities for terms such as: heat, pain-related, and nociceptive (posterior probabilities for these terms ranged from 0.86 to 0.89). As a comparison point, an examination of the posterior probabilities for coordinates within the ventral striatum (6, 8, −8), a region for

[1]These analyses are part of a larger set of analyses that are being compiled for a paper (M.D. Lieberman & N.I. Eisenberger, manuscript in preparation).

Figure 3

Reverse inference maps obtained from neurosynth.org for the search terms pain, control, conflict, error, and salience. Each map shows the neural regions (*red*) that are more specific to that search term than to other search terms.



which reward-related reverse inferences are typically accepted, reveals values of 0.90 and 0.91 for terms such as reward or rewards. Hence, although many different kinds of processes and tasks can activate regions such as the dACC and AI, this reverse inference analysis suggests that the most probable interpretation of this activity is consistent with the processing of pain.

Summary

To summarize, a careful review of the salience perspective suggests that (*a*) the term salience may not account for any additional variance that is not already accounted for by self-reported pain experience, (*b*) predictions made from the salience model have not been supported, and (*c*) the most likely interpretation of activity in the pain matrix seems to be pain. Interestingly, like the cognitive models of dACC function (Bush et al. 2000), the salience perspective seems to favor a more cognitive account of the activity of these regions over an affective or experiential one. It is possible that this account of the data is preferred because the term salience seems more objective—something that can be more easily measured and manipulated, just like luminosity, pitch, or weight. However, upon further reflection, salience may be just as subjective as pain experience. For example, the loud sound of construction going on outside one's office may be salient in one context, such as when trying to focus on an ongoing conversation, but not salient at all in another, such as when steeped in thought. Substituting a seemingly more objective account of what this set of neural regions responds to may not fully capture the true nature of what these regions are doing. In other words, for at least some of these regions, focusing on the subjective experience of unpleasantness or distress may be a more accurate account of the function of these regions.

WHAT DOES A PHYSICAL-SOCIAL PAIN OVERLAP MEAN FOR OUR UNDERSTANDING OF PHYSICAL AND SOCIAL PAIN?

What can we conclude about the physical-social pain overlap from the studies reviewed here? Several conclusions can be agreed on, and several others require further research. First, there is consensus that physical pain and social pain are not the same experience. Thus, even though physical and social pains share some of the same underlying neural substrates, they are not interchangeable. Hence, people do not confuse a broken heart with a broken bone, just as they do not confuse a bee sting with a stomachache. However, there is a common experiential element to all of these experiences, and that is the affective component of pain—the distressing experience associated with these threats that motivates individuals to terminate or escape the negative stimulus (Eisenberger 2012, Eisenberger & Lieberman 2004, Eisenberger et al. 2003, MacDonald & Leary 2005).

Perhaps less agreed on, however, is whether the sensory component is necessary for being able to categorize an experience as painful. Thus, one might wonder if social pain can truly be likened to physical pain if it does not also share the sensory component of pain. There are several reasons, however, to suggest that the affective component of pain may be especially critical to the hurt feelings that are at the heart of socially painful experience. First, from an experiential perspective, if given the choice between (*a*) being able to localize a painful stimulus without it feeling bothersome or distressing or (*b*) not being able to localize a painful stimulus but feeling very bothered and distressed, most people would probably choose the former (the experience that does not include distress), suggesting that the affective component is more tightly coupled with the hurtful part of painful experience. This intuitive notion is also supported by research. Patients unable to experience the sensory component of pain, but with the affective component of pain intact, do not lose their ability to feel the pain of social loss (Danziger & Willer 2005).

Still, future research is needed to determine the extent to which social and physical pain overlap in the sensory component of pain and what this overlap means. Some researchers have suggested that social pain activates neural regions involved in coding the sensory component of pain when the experience of social pain is intense, such as when reliving a recent relationship breakup (Kross et al. 2011). Future work is needed to more fully examine this hypothesis. It will also be important to further investigate how these sensory-related activations correlate with the experience of social pain. Does greater sensory-related neural activity correlate with greater self-reported distress, or is this type of neural activity more tightly correlated with reports of physical sensations (painful heart, upset stomach)? Finally, it will be important to identify whether certain kinds of painful sensations best map onto social pain (burning, aching, stabbing). Identifying the specific kinds of socially painful experiences that activate sensory-related neural regions and the psychological meaning of these activations will be critical for examining the extent of the physical-social pain overlap.

Identifying Boundary Conditions

Another important goal for future study is to determine the boundary conditions for what types of experiences activate pain-related neural regions. Research has shown that experiences of social pain activate affective pain-related regions, but accumulating evidence demonstrates that various types of negative affective experiences activate these regions as well. These findings bring up numerous important questions, such as: Is activity in the dACC/AI associated with any kind of negative affective state or only with a certain kind of negative affective state? For example, does activity in the dACC/AI stem from negative affect related to threats to survival-relevant goals (e.g., social exclusion and physical harm), or can it stem from threats to less survival-relevant goals as well (e.g., losing money)? In addition, given that many different types of negative experiences may activate these same regions, it may be advisable to use complementary methods, in addition to neuroimaging, to better understand whether there is something special about social pain or whether social pain represents one of many important goals that, if not met, would activate the affective pain matrix. For example, although both social rejection and losing money could be shown to activate the dACC and AI, it is possible that other techniques, such as fear conditioning, could determine whether social pain is a primary (unconditioned) punishing stimulus whereas losing money is a secondary (conditioned) punishing stimulus.

Lessons to Be Learned from a Physical-Social Pain Overlap

The study of the physical-social pain overlap provides some important lessons for our understanding of both emotional and pain processes. With respect to the understanding of emotions, emotion researchers have typically not included pain as an emotion because it has been seen as being more like a physical sensation, such as an itch or hunger. However, this separation of pain from other kinds of emotions may be a mistake stemming from the tendency to see pain as more physical than affective in nature and the historic tendency to lump physical pain with other exteroceptive modalities such as touch rather than interoceptive modalities such as temperature, which are typically experienced as valenced. Although pain may not be an emotion in the classic sense, it certainly shares features of emotional processes, including experiences of arousal and valence and a motivation to engage in action. Indeed, this basic experience of affective or pain distress may serve as a building block for various types of emotional experiences (Craig 2002, 2003; Panksepp 1998).

On the other side, studying the physical-social pain overlap may also change our understanding of physical pain. There is a strong tendency among those who study and treat pain to view pain

as a physical phenomenon that is caused by damage to the body. Nonetheless, years of research have shown that there can be tissue damage with no pain (e.g., wounded soldiers in battle) as well as severe pain with no tissue damage (e.g., migraines, fibromyalgia). These dissociations illustrate that, from an experiential perspective, the critical component of painful experience may stem from the mental experience of suffering. Focusing on the affective experience of pain could change how pain is conceptualized and treated. Currently, physical pain that stems from tissue damage occupies priority in terms of medical treatment goals, whereas pain that does not include tissue damage (e.g., fibromyalgia) is granted less attention, with patients often feeling that their suffering is being questioned. Social pain is similarly conceptualized as being outside the purview of medical attention because it seems more psychological or emotional than physical. Focusing on treating the affective component of pain might serve to level this playing field, putting the need to treat various types of physical and social pains at the same level of importance and perhaps providing new avenues for treatment.

CONCLUSIONS

It has long been suggested that many different kinds of painful experiences—including experiences of physical and social pain—share underlying commonalities. In fact, over 2,000 years ago, the Greek poet Antiphanes wrote, "All pain is one malady with many names." However, not until the past several decades have researchers started to explore whether physical and social pain share more than just metaphorical similarity. Indeed, although there is still much more to be explored, considerable evidence from human and animal research supports the hypothesis that physical and social pain rely on shared neural and neurochemical substrates. Although surprising in some ways, this co-opting of the primitive physical pain signal to indicate the possibility of broken social bonds highlights the critical role that social ties have played in the survival of our species. Continuing to explore the nature of this overlap may help us to more fully understand the depth of our social nature and to uncover the multiple ways in which our minds and bodies are inherently regulated by our social world.

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